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(71) Applicant: AMERICAN HEALTH PRODUCTS CORPORATION [US/US]; S.E. Financial Center, Suite 4370, 200 South Biscayne Boulevard, Miami, FL 33131 (US).

(72) Inventors: FROST, Phillip ; 125 East San Marino Drive, Miami Beach, FL 33139 (US). HSIAO, Charles, H. ; 4890 S.W. 104th Avenue, Cooper City, FL 33328 (US).

(74) Agent: WEGNER, Harold, C.; Wegner & Bretschneider, P.O. Box 18218, Washington, DC 20036-8218 (US).

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(54) Title: 2',3'-DIDESOXYADENOSINE COMPOSITION

(57) Abstract

A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesosxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.

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2' 3'-DIDESOXYADENOSINE COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions useful in the oral treatment of Acquired Immune Deficiency Syndrome.

2',3'-didesoxyadenosine is a known compound. Methylmethacrylates are known as coatings for pharmaceuticals, including Eudragit polymers of Rohm Pharma. Hydroxypropylmethylcellulose is known as a sustained release matrix, as disclosed first by Christenson et al., U.S. Patent 3,065,143 and again by Schor et al., U.S. Patent 4,389,393.

DESCRIPTION OF THE INVENTION

In accordance with a first aspect of the present invention there is provided a pharmaceutical composition for the treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine. Acquired immune deficiency syndrome was found by a prior researcher to be treated <u>in vitro</u>, but not <u>in vivo</u>, with 2',3'-didesoxyadenosine. According to the present invention, the 2',3'-didesoxyadenosine is permitted to remain free of degradation that apparently takes place in the stomach fluids by blocking contact of the 2',3'-didesoxyadenosine with the stomach fluids through said outer pharmaceutically inert component stable in acidic pH.

In a preferred aspect, there is provided a plurality of dosage subunits each having at least three components

including a component of 2',3'-didesoxyadenosine sandwiched between pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine. As an inner layer remote from the gastrointestinal fluids may be mentioned a nonpareil seed.

In a still further embodiment of this aspect of the invention there is provided a capsule containing said plurality of dosage subunits. As an alternative embodiment, there is provided a compressed tablet containing said plurality of dosage subunits, the matrix of said tablet disintegrating in the gastrointestinal tract to yield said plurality of dosage subunits.

In accordance with a second aspect of the present invention there is provided a pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a component of 2',3'-didesoxyadenosine and a barrier component to shield the 2',3'-didesoxyadenosine from the gastrointestinal fluids until said pharmaceutical composition passes into the small intestine, said barrier component being substantially impervious to degradation in a fluid other than a basic medium, whereby upon introduction into the gastrointestinal tract beyond the stomach said 2',3'-didesoxyadenosine is released.

In a third aspect of the present invention there is provided a sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-

didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits releasing said 2',3'-didesoxyadenosine only over a prolonged period of time.

In accordance with this third aspect of the present invention there is provided a sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which only erodes in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, at least some of said dosage subunits including an outer core of a slowly erodible polymeric material, whereby a sustained release of 2',3'-didesoxyadenosine is achieved.

In an alternate embodiment, there is provided a sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits

being contained in a matrix of a polymer which only gradually exposes said dosage subunits to the environment of the gastrointestinal tract. In one embodiment, the polymer is a hydroxypropylmethylcellulose, with a tablet made up of from about 60 to 95 percent, and preferably 80 to 92 percent by weight of said dosage subunits and from about 5 to about 40 percent, and preferably from about 8 to about 20 percent of the hydroxypropylmethyl-cellulose. As a hydroxypropylmethylcellulose suitable for the present invention may be mentioned Methocel K15M (Dow Chemical Co., Midland, Michigan) and Methocel K4M (Dow Chemical Co., Midland, Michigan).

A total adult daily dosage which is spread out over three to five administrations per day, or twice daily in the sustained release aspect of the present invention, comprises from about 2 to about 1000 mg per day, preferably about 25 to about 750 mg per day, and still more preferably about 10 to 250 mg per administration.

EXAMPLE I

Nonpareil seeds (20 to 30 mesh) are wetted with polyvinylpyrrolidone solution using Kollidon 30 (BASF, mw 30,000) which has been first dissolved in isopropanol in a coating pan with repeated dustings of 2',3'-didesoxyadenosine (about ten to twenty times) to build up a 2',3'-didesoxyadenosine-coated nonpareil seed.

EXAMPLE II

Alcohol dissolved Kollidone 90 (BASF, mw 90,000) is used as a wetting agent for nonpareil seeds (20 to 30 mesh) in a coating pan with repeated dustings of 2',3'-didesoxyadenosine (about ten to twenty times) to build up a 2',3'-didesoxyadenosine-coated nonpareil seed.

EXAMPLE III

The 2',3'-didesoxyadenosine-coated nonpareil seeds of Example I are introduced into a Wurster column (Glatt) and

coated with a methylmethacrylate in a solvent, using 50 gm Eudrigit L (Rohm Pharma) in a solvent mixture of 250 cc acetone and 250 cc isopropanol. After coating in the Wurster column, the total weight of 2',3'-didesoxyadenosine as a percentage of 2',3'-didesoxyadenosine plus coating is 45%. The dosage subunits dissolve readily in the small intestine.

EXAMPLE IV

2',3'-Didesoxyadenosine-coated nonpareil seeds of Example I are introduced into a Wurster column (Glatt) and coated with a methylmethacrylate in a solvent, using 25 gm Eudrigit L (Rohm Pharma), 25 gm Eudragit RS (Rohm Pharma) in a solvent mixture of 250 cc acetone and 250 cc isopropanol. After coating in the Wurster column, the total weight of 2',3'-didesoxyadenosine as a percentage of 2',3'-didesoxyadenosine plus coating is 45%. The inclusion of the Eudrigit RS retards dissolution of the dosage subunits to permit a sustained delivery of the 2',3'-didesoxyadenosine into the bloodstream of the patient.

EXAMPLE V

Capsules are made of a plurality of dosage subunits of Example III to make up 250 mg 2',3'-didesoxyadenosine per capsule. The capsules dissolve in the gastrointestinal tract upon oral administration, and each of the dosage subunits releases 2',3'-didesoxyadenosine in the small intestine, to provide 2',3'-didesoxyadenosine to the bloodstream.

EXAMPLE VI

Sustained release capsules are made of a plurality of dosage subunits of Example IV to make up 250 mg 2',3'-didesoxyadenosine per capsule. The capsules dissolve in the gastrointestinal tract upon oral administration, and each of the dosage subunits releases 2',3'-didesoxyadenosine in the small intestine, to provide 2',3'-

didesoxyadenosine to the bloodstream of the subject.

EXAMPLE VII

Tablets of a total weight of 330 mg are produced by mixing and then compressing together in a ratio of 10:1 of the dosage subunits of Example II and hydroxypropylmethylcellulose (Methocel K15M, Dow Chemical Co., Midland Michigan).

The sustained release tablet of this example provides an advantage over the other dosage forms in that the dosage subunits are only gradually exposed to the environment of the gastrointestinal fluids, whereby 2',3'-didesoxyadenosine is introduced into the bloodstream over a prolonged period of time.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.

2. A pharmaceutical composition of claim 1 for the oral treatment of acquired immune deficiency syndrome which comprises a plurality of dosage subunits each having at least three components including a component of 2',3'-didesoxyadenosine sandwiched between pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine.

3. A 2',3'-didesoxyadenosine pharmaceutical composition of claim 1 for the oral treatment of acquired immune deficiency syndrome which is a capsule containing said plurality of dosage subunits.

4. A pharmaceutical composition of claim 1 which is a compressed tablet containing said plurality of dosage subunits, the matrix of said tablet disintegrating in the gastrointestinal tract to yield said plurality of dosage subunits.

5. A pharmaceutical composition for the oral treatment of acquired immune deficiency syndrome which comprises a component of 2',3'-didesoxyadenosine and a barrier component to shield the 2',3'-didesoxyadenosine from the gastrointestinal fluids until said pharmaceutical

composition passes into the small intestine, said barrier component being substantially impervious to degradation in a fluid other than a basic medium, whereby upon introduction into the gastrointestinal tract beyond the stomach said 2',3'-didesoxyadenosine is released.

6. A sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits releasing said 2',3'-didesoxyadenosine only over a prolonged period of time.

7. A sustained release composition for the introduction of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which only erodes in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, at least some of said dosage subunits including an outer core of a slowly erodible polymeric material, whereby a sustained release of 2',3'-didesoxyadenosine is achieved.

8. A sustained release composition for the introduction

of 2',3'-didesoxyadenosine into the bloodstream of a patient suffering from acquired immune deficiency syndrome over a period of at least eight hours which comprises a plurality of dosage subunits each having at least two components including a component of 2',3'-didesoxyadenosine and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the 2',3'-didesoxyadenosine is not exposed to gastrointestinal fluids until the small intestine, said dosage subunits being contained in a matrix of a polymer which only gradually exposes said dosage subunits to the environment of the gastrointestinal tract.

9. A sustained release composition of claim 8 wherein said polymer is a hydroxypropylmethylcellulose.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02530

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/70; A 61 K 9/54; A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K; C 07 H

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P,X	EP, A, 0206497 (THE WELLCOME FOUNDATION LTD) 30 December 1986, see page 1, lines 1-26; page 4, ligne 23; page 6, lines 11-32; page 12, formulation F; page 13, formulation E	1-9
Y	Chemical Abstracts, volume 104, no. 21, 26 May 1986, (Columbus, Ohio, US), H. Mitsuya et al.: "Inhibition of the in vitro infectivity and cytophatic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxy-nucleosides", see page 352, abstract 183216h, & Proc. Natl. Acad. Sci. U.S.A. 1986, 83(6), 1911-15	1-9
Y	EP, A, 0136464 (BIOSEARCH S.p.A.) 10 April 1985, see pages 1,2; page 13, line 9 - page 15, line 20; claims	1-9
Y	EP, A, 0032562 (Dr Karl THOMAE GmbH) 29 July 1981, see pages 21,22; examples	1-8

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th January 1988	19 FEB 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	6, A), B), C), D); page 24, example 9; page 25, example 10; claims 1,5,8,9, 11,12	
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Y	WO, A, 84/02843 (EGYT GYOGYSZERVEGYESZETI GYAR) 2 August 1984, see the abstract	8,9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702530 SA 19151

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/02/88
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